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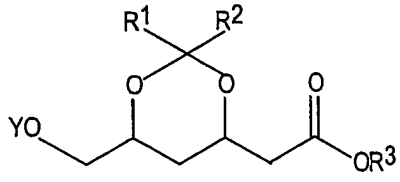
(54) Title: PROCESS FOR THE PREPARATION OF 2-(6-SUBSTITUTED-1,3-DIOXANE-4-YL) ACETIC ACID DERIVATES

(57) Abstract: The invention relates to a process for the conversion of group X in a 2-6(-substituted)-1,3-dioxane-4yl) acetic acid derivative according to formula 2 into a group OY in the presence of a phase transfer catalyst and an oxylating agent, by using as a phase transfer catalyst a quarternary phosphonium ion and by using as an oxylating agent an OY ion. X stands for a halogen and R^1 and R^2 and R^3 are each independently a C1-4 alkygroup or R^1 and R^2 together with the C-atom to which they are bound form a 5- or 6-membered cycloalkyl; Y stands for R^A-CO- or for R^B-SO_2- with R^A, R^B are chosen from the group of alkyl or aryl with 1-12 C-atoms.

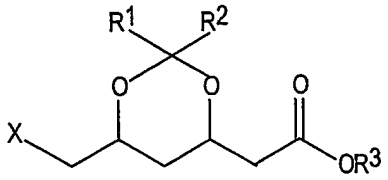
PROCESS FOR PREPARATION OF 2- (6-SUBSTITUTED -1, 3-DIOXANE-4-YL) ACETIC ACID DERIVATES

The invention relates to a process for the preparation of a 2-(6-substituted)-1,3-dioxane-4-yl) acetic acid derivative according to formula 1,



(1)

wherein R^1, R^2 and R^3 are each independently a C1-4 alkylgroup or wherein R^1 and R^2 together with the C-atom to which they are bound form a 5- or 6-membered cycloalkyl and wherein Y stands for R^A-CO- or for R^B-SO_2- with R^A, R^B are chosen from the group of alkyl or aryl with 1-12 C-atoms, from its corresponding 2-(6-substituted)-1,3-dioxane-4-yl) acetic acid derivative according to formula 2,



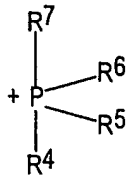
(2)

wherein R^1, R^2 and R^3 are as defined above and wherein X stands for a halogen, in the presence of a phase transfer catalyst and an oxylating agent.

Such a process is known from EP 1 024 139, wherein the preparation of a compound according to formula 1 from a compound according to formula 2 is achieved in the presence of a quaternary ammonium salt (phase transfer catalyst) and a carboxylic acid salt (acyloxylating agent).

It is the object of the invention to provide an alternative process for the preparation of a 2-(6-substituted)-1,3-dioxane-4-yl) acetic acid derivative according to formula 1 from its corresponding 2-(6-substituted)-1,3-dioxane-4-yl) acetic acid derivative according to formula 2.

This is achieved according to the invention by using a quarternary phosphonium ion according to formula 3 as a phase transfer catalyst,



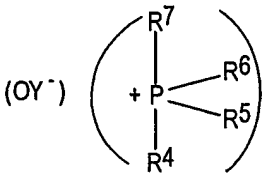
(3)

wherein R^4, R^5, R^6, R^7 each independently stand for an alkyl, cycloalkyl, aralkyl or aryl with 1 to 12 C-atoms, and an ion according to formula 4,

$$OY^- \qquad (4)$$

wherein Y is as defined above, as an oxylating agent. The reaction has a high yield.

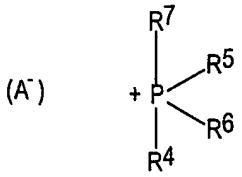
The quarternary phosphonium ion according to formula 3 used as a phase transfer catalyst and the ion according to formula 4 used as an oxylating agent may be present in a quarternary phosphonium salt according to formula 5,



(5)

wherein Y, R^4, R^5, R^6 and R^7 are as defined above. The phosphonium salt according to formula 5 can be used as both a phase transfer catalyst and as an oxylating agent. The quarternary phosphonium salt according to formula 5 can be prepared according to methods known to the person skilled in the art (e.g. analogous to the preparation of tetra-n-butylammoniumacetate as described in US 5 278 313).

In a preferred embodiment of the invention, the phase transfer catalyst and the oxylating agent are not present in the same molecule. In this embodiment, a quarternary phosphonium salt according to formula 3a,



(3a)

wherein R^4, R^5, R^6 and R^7 are as defined above and wherein A stands for the anion of the quarternary phopshoniumsalt and is selected from the group of halogens, for example Cl, Br, I is used as a phase transfer catalyst and the acid salt according to formula 4a,

$$(OY^-)_n \; M^{n+} \qquad (4a)$$

wherein Y is as defined above, wherein M stands for alkali metal or an alkaline metal,

for example Li, K, Na, Mg, Ca, Ba and wherein n represents an integer of 1 or 2, depending on the valence of M is used as an oxylating agent. Preferred is M is K or Na.

In the process according to the invention, halogens X are preferably Cl, Br or I, more preferably Cl.

In the process according to the invention, R^1, R^2 and R^3 are preferably a C1-4 alkyl group, more preferably R^1 and R^2 are a methyl or an ethyl group, more preferably a methyl group. R^3 is preferably a methyl or a butyl, most preferably a t-butyl.

In the process according to the invention Y groups are preferably represented by R^A-CO- or R^B-SO_2-, wherein R^A, R^B are chosen from the group of C_1-C_4 alkyl or aryl with 6-10 C-atoms. In a preferred embodiment, Y is chosen from the group of acyl, more preferably acetyl (with R^A is CH_3), benzenesulphonyl (with R^B is benzene), more preferably nitro substituted benzenesulphonyl (with R^B is p-nitro-benzene), tosyl (with R^B is p-methyl-benzene) or mesyl (with R^B is methyl).

In the process according to the invention, preferably a phosphonium salt according to formula 3a or according to formula 5, with at least three out of four R groups are the same (e.g. R^4, R^5, R^6 are butyl and R^7 is methyl or R^4, R^5, R^6 are phenyl and R^7 is butyl), more preferably a phosphonium salt with all four R groups are the same, is used.

R^A and R^B and R^4, R^5, R^6, R^7, -in case R^4, R^5, R^6, R^7 are aryl or aralkyl-, may be substituted for example with substituents chosen from the group of halogens, alkoxy (e.g. methoxy or ethoxy) with 1-6 C-atoms, alkyl with 1-6 C atoms, (e.g. methyl if R^B is toluene) or nitro, preferably only R^A or R^B are substituted.

The quarternary phosphonium salt according to formula 3a is preferably used in a molar equivalent amount of 0.01 to 1.0, more preferably 0.05 to 0.7, most preferably 0.1 to 0.5 relative to the amount of compound according to formula 2.

The quarternary phosphonium salt according to formula 5 is preferably used in a molar equivalent amount of 0.8 to 5, preferably 1 to 3, most preferably 1 to 1.5.

The acid salt according to formula 4a is preferably used in a molar equivalent amount of 1 to 5 relative to the amount of compound according to formula 2 present. More preferably, a molar equivalent amount of acid salt according to formula 4a of 1 to 4, most preferably 2 to 3, is used.

The solvents suitable for use in the present invention are a various

number of organic solvents, which are known to the person skilled in the art. Organic solvents, which may be used are hydrocarbon series solvents, for example benzene, toluene, cyclohexane, etc.; ether series solvents, for example diethyl ether tetrahydrofuran, 1,4-dioxane, methyl-t-butyl ether, dimethoxyethane, etc.; ester series solvents, for example ethyl acetate, butyl acetate, etc.; halogen containing solvents, for example methylene chloride, chloroform, 1,1,1-trichloroethane, etc.; nitrogen-containing solvents, for example acetamide, formamide, acetonitrile etc.; and aprotic polar solvents, for example dimethyl sulfoxide, N,N-dimethylformamide, N-methylpyrrolidone, hexamethylphosphoric triamide etc. Preferably, the solvent used is an aprotic polar solvent, more preferably the solvent used is N-methylpyrrolidone or N.N-dimethylformamide. The solvent can be used alone or in combination with one or more other solvent species, for example N-methylpyrrolidone in combination with toluene.

The temperature, by which the process of the invention is preferably carried out, is between 80 and 200°C, more preferably between 100 and 160°C, most preferably between 110 and 150°C.

The reaction product can be isolated from the reaction medium, if desired, according to methods known to the person skilled in the art (e.g. the method as described in US 5 278 313).

The invention will be illustrated by way of the following examples. However, these examples are not meant to restrict the invention.

Examples

Example 1

0.5 molar equivalents tetrabutylphosphoniumbromide (TBPB) and 2.5 molar equivalents potassiumacetate were added to a solution of I (tert-butyl 2-[(4R,6S)-6-(chloromethyl)-2,2-dimethyl-1,3-dioxan-4-yl]acetate in the solvent N-methylpyrrolidone (1g/3ml) at 100°C. The conversion of I in the presence of TBPB was 87.6% after 20 hours reaction time, the conversion of I into II (tert-butyl 2-{(4R,6S)-2,2-dimethyl-6-[(methyl-carbonyloxy)methyl]-1,3-dioxan-4-yl} acetate) thereof being 90.3%.

Example 2

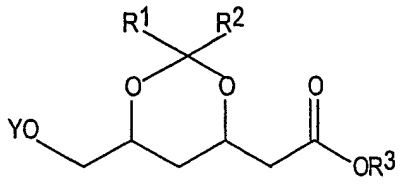
Example I was repeated whereby the reaction temperature for the conversion of I into II was kept at 115°C. The conversion of I in the presence of TBPB was 95.1% after 3 hours reaction time, the conversion of I into II thereof being 91%.

Example 3

0.1 molar equivalents tetraphenylphosphoniumbromide (TTB) and 2.5 molar equivalents potassiumacetate were added to a solution of I (tert-butyl 2-[(4R,6S)-6-(chloromethyl)-2,2-dimethyl-1,3-dioxan-4-yl]acetate in the solvent N-methylpyrrolidone (1g/3ml) at 140°C. After 20 hours, the conversion of I was 97%, the conversion of I into II thereof being 77.2%.

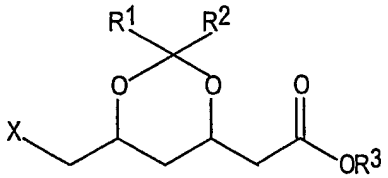
CLAIMS

1. Process for the preparation of a 2-(6-substituted)-1,3-dioxane-4-yl) acetic acid derivative according to formula 1,



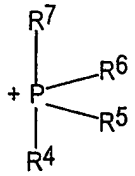
(1)

wherein R^1, R^2 and R^3 are each independently a C1-4 alkylgroup or wherein R^1 and R^2 together with the C-atom to which they are bound form a 5- or 6-membered cycloalkyl and wherein Y stands for R^A-CO- or for R^B-SO_2- with R^A, R^B are chosen from the group of alkyl or aryl with 1-12 C-atoms, from its corresponding 2-(6-substituted)-1,3-dioxane-4-yl) acetic acid derivative according to formula 2,



(2)

wherein R^1, R^2 and R^3 are as defined above and wherein X stands for a halogen, in the presence of a phase transfer catalyst and an oxylating agent, characterized in that a quarternary phosphonium ion according to formula 3,



(3)

wherein R^4, R^5, R^6, R^7 each independently stand for an alkyl, cycloalkyl, aralkyl or aryl with 1 to 12 C-atoms, is used as a phase transfer catalyst and an ion according to formula 4,

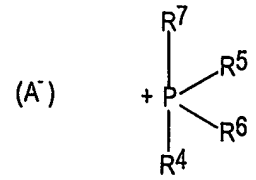
$$OY^- \qquad (4)$$

wherein Y is as defined above, is used as an oxylating agent.

2. Process according to claim 1, characterized in that R^A, R^B are chosen from the group of C_1-C_4 alkyl or aryl with 6-10 C-atoms.

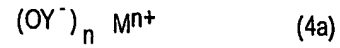
3. Process according to any of claims 1-2, characterized in that as a phase

transfer catalyst a quarternary phosphonium salt according to formula 3a,



(3a)

wherein R^4, R^5, R^6 and R^7 are as defined above and wherein A stands for a halogen, is used and in that an acid salt according to formula 4a,



(4a)

wherein Y is as defined above, wherein M stands for alkali metal or an alkaline metal, is used as an oxylating agent.

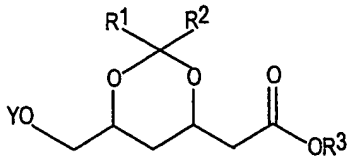
4. Process according to claim 3, characterized in that the quarternary phosphonium salt according to formula 3a is used in a molar equivalent amount of 0.05 to 0.7 relative to the amount of compound according to formula 2.

5. Process according to claim 4, characterized in that the quarternary phosphonium salt according to formula 3a is used in a molar equivalent amount of 0.1 to 0.5 relative to the amount of compound according to formula 2.

6. Process according to any of claims 1-5, characterized in that the process is carried out at a temperature between 100 and 160°C.

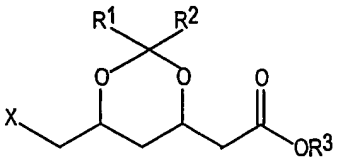
7. Process according to any of claims 1-6, characterized in that the process is carried out at a temperature between 110 and 150°C.

8. Process according to any of claims 1-7, characterized in that the compound according to formula 1 is tert-butyl 2-{(4R,6S)-2,2 dimethyl-6-[(methyl-carbonyloxy)methyl]-1,3-dioxan-4-yl} acetate and in that the compound according to formula 2 is tert-butyl 2-[(4R,6S)-6-(chloromethyl)-2,2-dimethyl-1,3-dioxan-4yl]acetate.



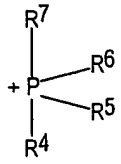
(1)

Formula 1



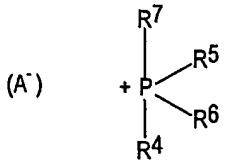
(2)

Formula 2



(3)

Formula 3



(3a)

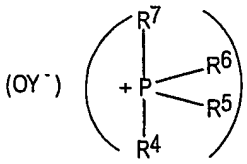
Formula 3a

OY^- (4)

Formula 4

$(OY^-)_n\ M^{n+}$ (4a)

Formula 4a



(5)

Formula 5

INTERNATIONAL SEARCH REPORT

PCT/NL 02/00876

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D319/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1 024 139 A (KANEGAFUCHI CHEMICAL IND) 2 August 2000 (2000-08-02) cited in the application page 15, line 20 -page 17, line 31; claims 1,17	1-8

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
7 March 2003	13/03/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Seelmann, I

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INTERNATIONAL SEARCH REPORT

PCT/NL 02/00876

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